

INTERNATIONAL COOPERATION TREATY

PCT

NOTIFICATION OF ELECTION

(PCT Rule 61.2)

From the INTERNATIONAL BUREAU

To:

Assistant Commissioner for Patents
United States Patent and Trademark
Office
Box PCT

Washington, D.C.20231
ETATS-UNIS D'AMERIQUE

in its capacity as elected Office

Date of mailing:

06 July 2000 (06.07.00)

International application No.:

PCT/EP99/10257

Applicant's or agent's file reference:

JAB 1461-PCT

International filing date:

20 December 1999 (20.12.99)

Priority date:

24 December 1998 (24.12.98)

Applicant:

MCGEE, John, Paul et al

1. The designated Office is hereby notified of its election made:



in the demand filed with the International preliminary Examining Authority on:

15 May 2000 (15.05.00)



in a notice effecting later election filed with the International Bureau on:

2. The election ☒ was



was not

made before the expiration of 19 months from the priority date or, where Rule 32 applies, within the time limit under Rule 32.2(b).

The International Bureau of WIPO
34, chemin des Colombettes
1211 Geneva 20, Switzerland

Facsimile No.: (41-22) 740.14.35

Authorized officer:

J. Zahra

Telephone No.: (41-22) 338.83.38

PATENT COOPERATION TREATY

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INTERNATIONAL SEARCH REPORT

(PCT Article 18 and Rules 43 and 44)

Applicant's or agent's file reference	FOR FURTHER ACTION <small>see Notification of Transmittal of International Search Report (Form PCT/ISA/220) as well as, where applicable, item 5 below.</small>	
JAB 1461-PCT		
International application No.	International filing date (day/month/year)	(Earliest) Priority Date (day/month/year)
PCT/EP 99/ 10257	20/12/1999	24/12/1998
Applicant		
JANSSEN PHARMACEUTICA N.V ET AL		

This International Search Report has been prepared by this International Searching Authority and is transmitted to the applicant according to Article 18. A copy is being transmitted to the International Bureau.

This International Search Report consists of a total of 3 sheets.

☒ It is also accompanied by a copy of each prior art document cited in this report.

1. Basis of the report

a. With regard to the language, the international search was carried out on the basis of the international application in the language in which it was filed, unless otherwise indicated under this item.

☐ the international search was carried out on the basis of a translation of the international application furnished to this Authority (Rule 23.1(b)).

b. With regard to any nucleotide and/or amino acid sequence disclosed in the international application, the international search was carried out on the basis of the sequence listing:

☐ contained in the international application in written form.

☐ filed together with the international application in computer readable form.

☐ furnished subsequently to this Authority in written form.

☐ furnished subsequently to this Authority in computer readable form.

☐ the statement that the subsequently furnished written sequence listing does not go beyond the disclosure in the international application as filed has been furnished.

☐ the statement that the information recorded in computer readable form is identical to the written sequence listing has been furnished.

2. ☒ Certain claims were found unsearchable (See Box I).

3. ☐ Unity of invention is lacking (see Box II).

4. With regard to the title,

☒ the text is approved as submitted by the applicant.

☐ the text has been established by this Authority to read as follows:

5. With regard to the abstract,

☒ the text is approved as submitted by the applicant.

☐ the text has been established, according to Rule 38.2(b), by this Authority as it appears in Box III. The applicant may, within one month from the date of mailing of this international search report, submit comments to this Authority.

6. The figure of the drawings to be published with the abstract is Figure No. _____

☐ as suggested by the applicant.

☐ because the applicant failed to suggest a figure.

☐ because this figure better characterizes the invention.

☐ None of the figures.

INTERNATIONAL SEARCH REPORT

International application No.

PCT/EP 99/ 10257

Box I Observations where certain claims were found unsearchable (Continuation of Item 1 of first sheet)

This International Search Report has not been established in respect of certain claims under Article 17(2)(a) for the following reasons:

1. ☒ Claims Nos.:
because they relate to subject matter not required to be searched by this Authority, namely:

Remark: Although claims 27-29 are directed to a method of treatment of the human/animal body, the search has been carried out and based on the alleged effects of the compound/composition.

2. ☐ Claims Nos.:
because they relate to parts of the International Application that do not comply with the prescribed requirements to such an extent that no meaningful International Search can be carried out, specifically:

3. ☐ Claims Nos.:
because they are dependent claims and are not drafted in accordance with the second and third sentences of Rule 6.4(a).

Box II Observations where unity of invention is lacking (Continuation of Item 2 of first sheet)

This International Searching Authority found multiple inventions in this International application, as follows:

1. ☐ As all required additional search fees were timely paid by the applicant, this International Search Report covers all searchable claims.
2. ☐ As all searchable claims could be searched without effort justifying an additional fee, this Authority did not invite payment of any additional fee.
3. ☐ As only some of the required additional search fees were timely paid by the applicant, this International Search Report covers only those claims for which fees were paid, specifically claims Nos.:
4. ☐ No required additional search fees were timely paid by the applicant. Consequently, this International Search Report is restricted to the invention first mentioned in the claims; it is covered by claims Nos.:

Remark on Protest

☐ The additional search fees were accompanied by the applicant's protest.

☐ No protest accompanied the payment of additional search fees.

INTERNATIONAL SEARCH REPORT

Intern nal Application No
PCT/EP 99/10257

A. CLASSIFICATION OF SUBJECT MATTER
IPC 7 A61K31/55 A61P25/28 A61K9/54

According to International Patent Classification (IPC) or to both national classification and IPC

B. FIELDS SEARCHED

Minimum documentation searched (classification system followed by classification symbols)

IPC 7 A61K A61P

Documentation searched other than minimum documentation to the extent that such documents are included in the fields searched

Electronic data base consulted during the international search (name of data base and, where practical, search terms used)

C. DOCUMENTS CONSIDERED TO BE RELEVANT

Category *	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
Y	CA 1 326 632 A (DAVIS ET AL) 1 February 1994 (1994-02-01) cited in the application the whole document	1-12, 14, 16-18, 21, 26-29
Y	US 5 213 811 A (FRISBEE ET ASL.) 25 May 1993 (1993-05-25)	1-12, 14, 16-18, 21, 26-29
A	the whole document EP 0 629 402 A (BAYER AG) 21 December 1994 (1994-12-21) page 12; example 9	1, 10, 11

☐ Further documents are listed in the continuation of box C.

☒ Patent family members are listed in annex.

* Special categories of cited documents :

- "A" document defining the general state of the art which is not considered to be of particular relevance
- "E" earlier document but published on or after the international filing date
- "L" document which may throw doubts on priority claim(s) or which is cited to establish the publication date of another citation or other special reason (as specified)
- "O" document referring to an oral disclosure, use, exhibition or other means
- "P" document published prior to the international filing date but later than the priority date claimed

- "T" later document published after the international filing date or priority date and not in conflict with the application but cited to understand the principle or theory underlying the invention
- "X" document of particular relevance; the claimed invention cannot be considered novel or cannot be considered to involve an inventive step when the document is taken alone
- "Y" document of particular relevance; the claimed invention cannot be considered to involve an inventive step when the document is combined with one or more other such documents, such combination being obvious to a person skilled in the art.
- "&" document member of the same patent family

Date of the actual completion of the international search

11 May 2000

Date of mailing of the international search report

17/05/2000

Name and mailing address of the ISA

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Fax: (+31-70) 340-3016

Authorized officer

Benz, K

INTERNATIONAL SEARCH REPORT

International application No.

PCT/EP 99/10257

Box I Observations where certain claims were found unsearchable (Continuation of item 1 of first sheet)

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because they relate to subject matter not required to be searched by this Authority, namely:
Remark: Although claims 27-29 are directed to a method of treatment of the human/animal body, the search has been carried out and based on the alleged effects of the compound/composition.
2. ☐ Claims Nos.:
because they relate to parts of the International Application that do not comply with the prescribed requirements to such an extent that no meaningful International Search can be carried out, specifically:
3. ☐ Claims Nos.:
because they are dependent claims and are not drafted in accordance with the second and third sentences of Rule 6.4(a).

Box II Observations where unity of invention is lacking (Continuation of item 2 of first sheet)

This International Searching Authority found multiple inventions in this international application, as follows:

1. ☐ As all required additional search fees were timely paid by the applicant, this International Search Report covers all searchable claims.
2. ☐ As all searchable claims could be searched without effort justifying an additional fee, this Authority did not invite payment of any additional fee.
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4. ☐ No required additional search fees were timely paid by the applicant. Consequently, this International Search Report is restricted to the invention first mentioned in the claims; it is covered by claims Nos.:

Remark on Protest

- ☐ The additional search fees were accompanied by the applicant's protest.
- ☐ No protest accompanied the payment of additional search fees.

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INTERNATIONAL SEARCH REPORT

information on patent family members

International Application No

PCT/EP 99/10257

Patent document cited in search report	Publication date	Patent family member(s)	Publication date
CA 1326632 A	01-02-1994	CA 1338326 A AU 632458 B AU 1808488 A JP 2503794 T JP 2755403 B WO 8808708 A DK 549189 A EP 0363415 A FI 102756 B	14-05-1996 07-01-1993 06-12-1988 08-11-1990 20-05-1998 17-11-1988 03-01-1990 18-04-1990 15-02-1999
US 5213811 A	25-05-1993	NONE	
EP 629402 A	21-12-1994	DE 4319760 A AU 6345794 A CA 2125620 A CN 1099263 A CZ 9401464 A FI 942803 A HU 70759 A JP 6345649 A NO 942228 A NZ 260732 A PL 303822 A SK 72494 A ZA 9404187 A	22-12-1994 22-12-1994 16-12-1994 01-03-1995 18-01-1995 16-12-1994 30-10-1995 20-12-1994 16-12-1994 27-02-1996 09-01-1995 12-04-1995 08-02-1995

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INTERNATIONAL APPLICATION PUBLISHED UNDER THE PATENT COOPERATION TREATY (PCT)

(51) International Patent Classification ⁷ : A61K 31/55, A61P 25/28, A61K 9/54	A1	(11) International Publication Number: WO 00/38686 (43) International Publication Date: 6 July 2000 (06.07.00)
(21) International Application Number: PCT/EP99/10257	(74) Agent: QUAGHEBEUR, Luc; Janssen Pharmaceutica N.V., Patent Department, Turnhoutseweg 30, B-2340 Beerse (BE).	
(22) International Filing Date: 20 December 1999 (20.12.99)		
(30) Priority Data: 98204447.1 24 December 1998 (24.12.98) EP		
(71) Applicant (for all designated States except US): JANSSEN PHARMACEUTICA N.V. [BE/BE]; Patent Department, Turnhoutseweg 30, B-2340 Beerse (BE).		
(72) Inventors; and		
(75) Inventors/Applicants (for US only): MCGEE, John, Paul [GB/BE]; Janssen Pharmaceutica N.V., Turnhoutseweg 30, B-2340 Beerse (BE). GILIS, Paul, Marie, Victor [BE/BE]; Janssen Pharmaceutica N.V., Turnhoutseweg 30, B-2340 Beerse (BE). DE WEER, Marc, Maurice, Germain [BE/BE]; Janssen Pharmaceutica N.V., Turnhoutseweg 30, B-2340 Beerse (BE). DE CONDÉ, Valentin, Florent, Victor [BE/BE]; Janssen Pharmaceutica N.V., Turnhoutseweg 30, B-2340 Beerse (BE). DE BRUIJN, Herman, Johannes, Catherina [BE/BE]; Janssen Pharmaceutica N.V., Turnhoutseweg 30, B-2340 Beerse (BE). VAN DYCKE, Frederic, Anne, Rodolf [BE/BE]; Janssen Pharmaceutica N.V., Turnhoutseweg 30, B-2340 Beerse (BE).	(81) Designated States: AE, AL, AM, AT, AU, AZ, BA, BB, BG, BR, BY, CA, CH, CN, CR, CU, CZ, DE, DK, DM, EE, ES, FI, GB, GD, GE, GH, GM, HR, HU, ID, IL, IN, IS, JP, KE, KG, KP, KR, KZ, LC, LK, LR, LS, LT, LU, LV, MA, MD, MG, MK, MN, MW, MX, NO, NZ, PL, PT, RO, RU, SD, SE, SG, SI, SK, SL, TJ, TM, TR, TT, TZ, UA, UG, US, UZ, VN, YU, ZA, ZW, ARIPO patent (GH, GM, KE, LS, MW, SD, SL, SZ, TZ, UG, ZW), Eurasian patent (AM, AZ, BY, KG, KZ, MD, RU, TJ, TM), European patent (AT, BE, CH, CY, DE, DK, ES, FI, FR, GB, GR, IE, IT, LU, MC, NL, PT, SE), OAPI patent (BF, BJ, CF, CG, CI, CM, GA, GN, GW, ML, MR, NE, SN, TD, TG).	
(54) Title: CONTROLLED RELEASE GALANTAMINE COMPOSITION		
(57) Abstract		
<p>The present invention is concerned with controlled release compositions for oral administration comprising galantamine; and with processes of preparing such controlled release compositions.</p>		

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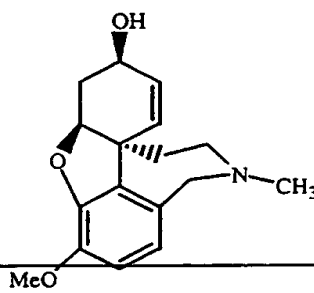
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CONTROLLED RELEASE GALANTAMINE COMPOSITION

The present invention is concerned with controlled release compositions for oral

- 5 administration comprising galantamine ; and with processes of preparing such controlled release compositions.

Galantamine (I), a tertiary alkaloid, has been isolated from the bulbs of the Caucasian snowdrops *Galanthus woronowi* (Proskurnina, N. F. and Yakoleva, A. P. 1952,
10 Alkaloids of *Galanthus woronowi*. II. Isolation of a new alkaloid. (In Russian.) Zh. Obschchei Khim. (J. Gen. Chem.) 22, 1899-1902). It has also been isolated from the common snowdrop *Galanthus nivalis* (Boit, 1954).



The chemical name of galantamine is [4aS-(4a α , 6 β , 8aR*)]-4a, 5, 9, 10, 11, 12-
15 hexahydro-3-methoxy-11-methyl-6H-benzofuro[3a, 3, 2-ef][2]benzazepin-6-ol ; both the base compound and its hydrobromide are laevorotatory. Galantamine is a well-known acetylcholinesterase inhibitor which is active at nicotinic receptor sites but not on muscarinic receptor sites. It is capable of passing the blood-brain barrier in humans, and presents no severe side effects in therapeutically effective dosages.

20 Galantamine has been used extensively as a curare reversal agent in anaesthetic practice in Eastern bloc countries (cf. review by Paskow, 1986) and also experimentally in the West (cf. Bretagne and Valetta, 1965; Wislicki, 1967; Consanitis, 1971).

25 Galantamine has been marketed by Waldheim (Sanochemia Gruppe) as NivalinTM in Germany and Austria since the 1970s for indications such as facial neuralgia.

The use of galantamine or an analogue or a pharmaceutically acceptable acid addition salt thereof for the preparation of a medicament for treating Alzheimer's Dementia
30 (AD) and related dementias has been described in EP-0,236,684 (US-4,663,318). This patent only has a generic disclosure of possible dosage forms of galantamine.

CA-1,326,632 generically discloses slow release formulations of galantamine.

The use of galantamine for treating alcoholism and the administration via a transdermal therapeutic system (TTS) or patch is disclosed in EP-0,449,247 and WO-94/16707.

5 Similarly, the use of galantamine in the treatment of nicotine dependence using administration via a transdermal therapeutic system (TTS) or patch is disclosed in WO-94/16708. Treatment of nerve gas poisoning is disclosed in DE-4,342,174.

10 A number of applications by E. Snorrason disclose the use of galantamine, analogues thereof and pharmaceutically acceptable salts thereof for the preparation of medicaments for treating mania (US-5,336,675), chronic fatigue syndrome (CFS) (EP-0,515,302 ; US-5,312,817), the negative effects of benzodiazepine treatment (EP-0,515,301) and the treatment of schizophrenia (US-5,633,238). In these applications and patents, e.g. in US-5,312,817, a number of immediate release tablet
15 formulations of galantamine hydrobromide are given.

WO-97/47304 discloses fast-dissolving or immediate release tablets of galantamine prepared by direct compression. These and other art-known immediate release tablets are administered twice (b.i.d.) or thrice (t.i.d.) daily with an interval of 8 hours. The
20 plasma levels of the active ingredient typically raise sharply (early T_{max} and relatively high C_{max}) and decline rapidly (deep trough after about 6 to 8 hours).

Therapy with galantamine can be considered optimal when effective plasma levels are reached when required. In addition, peak values (C_{max}) should be as low and level as
25 possible so as to reduce the incidence and severity of possible side effects. The foregoing requirements not only apply upon single dose administration, but also upon repeated dose administration (until a steady-state condition is reached). In particular, when treating a patient suffering from Alzheimer's Disease, optimum efficacy is expected when effective plasma levels are maintained during daytime; during nighttime
30 galantamine plasma levels probably may be lower. For the treatment of other conditions, for example for treating sleep disordered breathing such as snoring and apnoea (WO-97/22339), one may wish to attain the reverse situation, namely to have effective plasma levels during the night, and lower levels during daytime. For the benefit of the patient and the caretakers, a pharmaceutical dosage form that has to be
35 administered once daily only and yields effective plasma levels for eight hours (nighttime) to 16 hours (daytime) would be highly desirable.

The present invention relates to a controlled release formulation containing galantamine

as the active ingredient, characterized in that it comprises particles comprising galantamine or a pharmaceutically acceptable acid addition salt thereof, a water soluble pharmaceutically acceptable excipient and optionally other pharmaceutically acceptable excipients, said particles being coated by a release rate controlling membrane coating.

- 5 Dosage forms comprising a therapeutically effective amount of said controlled release formulations can be administered orally to a patient once daily. In preferred dosage forms, part of the galantamine is present in an immediate release form, for example, as particles lacking a release rate controlling membrane coating, or as immediate release minitabets, or as a topcoat on the controlled release formulation.

10

Preferably, the formulations according to the present invention comprise galantamine in the form of galantamine hydrobromide (1:1).

- 15 The water soluble excipient can conveniently be a film forming polymer. Useful water soluble film forming polymers are polymers that have an apparent viscosity of 1 to 100 mPa.s when dissolved in a 2 % aqueous solution at 20°C solution. For example, the water soluble polymer can be selected from the group comprising

- alkylcelluloses such as methylcellulose,
- ~~hydroxyalkylcelluloses such as hydroxymethylcellulose,~~
- 20 hydroxyethylcellulose, hydroxypropylcellulose and hydroxybutylcellulose,
- hydroxyalkyl alkylcelluloses such as hydroxyethyl methylcellulose and hydroxypropyl methylcellulose,
- carboxyalkylcelluloses such as carboxymethylcellulose,
- alkali metal salts of carboxyalkylcelluloses such as sodium carboxymethyl-
- 25 cellulose,
- carboxyalkyl alkylcelluloses such as carboxymethyl ethylcellulose,
- carboxyalkylcellulose esters,
- starches,
- pectines such as sodium carboxymethylamylopectine,
- 30 - chitine derivatives such as chitosan,
- polysaccharides such as alginic acid, alkali metal and ammonium salts thereof, carrageenans, galactomannans, tragacanth, agar-agar, gummi arabicum, guar gummi and xanthan gummi,
- polyacrylic acids and the salts thereof,
- 35 - polymethacrylic acids and the salts thereof, methacrylate copolymers,
- polyvinylalcohol,
- polyvinylpyrrolidone, copolymers of polyvinylpyrrolidone with vinyl acetate

- polyalkylene oxides such as polyethylene oxide and polypropylene oxide and copolymers of ethylene oxide and propylene oxide.

Non-enumerated polymers which are pharmaceutically acceptable and have appropriate physico-chemical properties as defined hereinbefore are equally suited for preparing

5 particles according to the present invention.

Preferred water-soluble polymers are for example hydroxypropyl methylcellulose (Methocel®, Pharmacoat®), polymethacrylate (Eudragit E®), hydroxypropylcellulose (Klucel®), or a polyvidone. Especially preferred water-soluble polymers are
10 hydroxypropyl methylcelluloses or HPMC. Said HPMC contains sufficient hydroxypropyl and methoxy groups to render it water-soluble. HPMC having a methoxy degree of substitution from about 0.8 to about 2.5 and a hydroxypropyl molar substitution from about 0.05 to about 3.0 are generally water-soluble. Methoxy degree of substitution refers to the average number of methyl ether groups present per
15 anhydroglucose unit of the cellulose molecule. Hydroxypropyl molar substitution refers to the average number of moles of propylene oxide which have reacted with each anhydroglucose unit of the cellulose molecule. Hydroxypropyl methylcellulose is the United States Adopted Name for hypromellose (see Martindale, The Extra Pharmacopoeia, 29th edition, page 1435). Preferably hydroxypropyl methylcellulose
20 with low viscosity, i.e. about 5 mPa.s, is used, e.g. hydroxypropyl methylcellulose 2910 5 mPa.s. In the four digit number "2910", the first two digits represent the approximate percentage of methoxyl groups and the third and fourth digits the approximate percentage composition of hydroxypropoxyl groups. 5 mPa.s is a value indicative of the apparent viscosity of a 2 % aqueous solution at 20°C.

25 Suitable HPMC include those having a viscosity from about 1 to about 100 mPa.s, in particular form about 3 to about 15 mPa.s, preferably about 5 mPa.s. The most preferred type of HPMC having a viscosity of 5 mPa.s., is the commercially available HPMC 2910 5 mPa.s. An equally preferred type of HPMC is admixed with
30 polyethylene glycol 400, commercially available from Colorcon (UK) as Opadry™ OY-7240 clear.

The weight-by-weight ratio of drug : polymer is in the range of 17 : 1 to 1 : 5, preferably 10 : 1 to 1 : 3. In the case of (galantamine.HBr) : (HPMC 2910 5 mPa.s),
35 said ratio may range from about 10 : 1 to about 1 : 3, and optimally is from 7 : 1 to 1 : 2. The weight-by-weight ratio of galantamine.HBr to other water-soluble polymers may be determined by a person skilled in the art by straightforward experimentation. The lower limit is determined by practical considerations.

In particular the present invention is concerned with particles which comprise (a) a central, rounded or spherical core, (b) a layer or a coating film of a water-soluble polymer and galantamine hydrobromide (1:1), (c) optionally a seal-coating polymer layer and (d) a release rate controlling membrane coating. The core has a diameter of about 250 to about 1,180 μm (16-60 mesh), preferably of about 600 to about 1,180 μm (16-30 mesh).

Pellets, beads or cores of the dimensions mentioned herein can be obtained by sieving through nominal standard test sieves as described in the CRC Handbook, 64th ed., page F-114. Nominal standard sieves are characterized by the mesh/hole width (μm), DIN 4188 (mm), ASTM E 11-70 (No), Tyler® (mesh) or BS 410 (mesh) standard values. Throughout this description and the claims, particle sizes are designated by reference to the mesh/hole width in μm and to the corresponding Sieve No in the ASTM E11-70 standard.

Materials suitable for use as cores in the particles according to the present invention are manifold, provided that said materials are pharmaceutically acceptable and have appropriate dimensions (about 16-60 mesh) and firmness. Examples of such materials are polymers e.g. plastic resins; inorganic substances, e.g. silica, glass, hydroxyapatite, salts (sodium or potassium chloride, calcium or magnesium carbonate) and the like; organic substances, e.g. activated carbon, acids (citric, fumaric, tartaric, ascorbic and the like acids), and saccharides and derivatives thereof. Particularly suitable materials are saccharides such as sugars, oligosaccharides, polysaccharides and their derivatives, for example, glucose, rhamnose, galactose, lactose, sucrose, mannitol, sorbitol, dextrin, maltodextrin, cellulose, microcrystalline cellulose, sodium carboxymethyl cellulose, starches (maize, rice, potato, wheat, tapioca) and the like saccharides.

A particularly preferred material suitable for use as cores in the particles according to the present invention is represented by 16-60 mesh sugar spheres (USP 22 / NF XVII, p. 1989) which consist of 62.5% - 91.5% (w/w) sucrose, the remainder being starch and possibly also dextrans, and which are pharmaceutically inert or neutral. Consequently, these cores are also known in the art as neutral pellets.

Depending on the weight-by-weight ratio of drug : polymer, the water-soluble polymer and galantamine are herein said to form either a layer (ratio > 10 : 1) or a coat or coating film (ratio < 10 : 1).

As an alternative to the drug layered or drug coated inert pellets described thus far, suitable particles comprising glantamine may also be formed by granules or by spheroids (spherical granules) prepared according to art-known methods of granulation and spheronization.

5 The release rate controlling membrane coating comprises a water insoluble polymer and optionally a plasticizer. Said polymer is ethylcellulose and the plasticizer is selected from the group comprising dibutyl sebacate, diethyl phthalate and triethyl citrate. It is useful to modify the properties of the water-insoluble polymer by the
10 addition of particular amounts of a water-soluble polymer as described hereinbefore, preferably HPMC. The addition of the water-soluble polymer is especially useful to increase the onset of action. For the particles according to the present invention, the ratio ethylcellulose : HPMC can vary from 100 : 0 to about 70 : 30, in particular from about 80 : 20 to about 72.5 : 27.5, more in particular from about 75 : 25 to about 72.5 :
15 27.5. The release rate controlling membrane coating may be applied to the drug coated cores in an aqueous dispersion (Aquacoat™, Surelease™), or as a solution in an organic solvent system. A useful organic system comprises an alcohol, *e.g.* methanol or ethanol, and optionally a chlorinated hydrocarbon such as for example dichloromethane.

20 The weight of the release rate controlling membrane coating ranges from 3 % to 15 % of the uncoated particle, in particular from about 4% to about 12 %. The rate of release of the active ingredient from the particles is approximately inversely proportional with the thickness of the release rate controlling membrane coating.

25 A seal coat lies optionally between the drug core and the release rate controlling membrane coating. The seal coating polymer layer is applied to the drug coated cores to prevent sticking of the particles during the process and to prevent migration of the drug into the the release rate controlling membrane. Preferably, a thin layer of HPMC
30 2910 5 mPa.s and polyethylene glycol (PEG), in particular polyethylene glycol 400 is used as a seal coating polymer layer.

In addition, the particles according to the present invention may further contain various additives such as thickening agents, lubricants, surfactants, preservatives, complexing
35 and chelating agents, electrolytes or other active ingredients.

The particles can be filled in hard-gelatin capsules such that a therapeutically effective amount of, for example, 8 to 32 mg of the active ingredient is available per dosage

form. An advantageous pharmacokinetic profile (fast onset, level peak and trough values) is obtained when from 70 to 80 % of the galantamine is comprised within the controlled release particles and the remaining 20 to 30 % of the galantamine is comprised in an immediate release form, preferably the controlled release particle amount to 75 % of the galantamine and the immediate release form to 25 %.

In order to achieve the desired pharmacokinetic, the dosage forms may be filled with particles that release the active ingredient at different rates, at least one kind that releases the active ingredient slowly, and at least one kind that releases the active ingredient more rapidly, in particular one kind that releases the active ingredient immediately, e.g. particles as described that lack the release rate controlling membrane. The different particles may be filled consecutively in the capsules, or they may be premixed and the thus obtained premix may be filled into the capsules (taking into account possible segregation).

Alternatively, the controlled release particles of the present invention may further comprise a top-coat of a water-soluble polymer as described hereinbefore and galantamine which is released practically immediately upon ingestion and thus ensures a rapid onset of action.

Another alternative solution for providing a dosage form with a pharmacokinetic profile as outlined, namely with a fast onset, level peak and trough values, comprises filling a capsule with controlled release particles as described hereinbefore (70 to 80 %, preferably 75 % of the galantamine dose) together with one or more minitablets which comprise the remaining 20 to 30 %, preferably 25 % of galantamine. Suitable immediate release tablet formulations of galantamine have been described previously in WO-97/47304.

The present invention also relates to processes of preparing formulations as described hereinbefore comprising admixing galantamine or a pharmaceutically acceptable salt form thereof with a water soluble excipient to form a drug core, optionally applying a seal coat to the drug core, and thereafter applying the release rate controlling membrane coating.

The particles according to the present invention are conveniently prepared in the following manner. A drug coating solution is prepared by dissolving into a suitable solvent system appropriate amounts of galantamine.HBr and a water-soluble polymer. A suitable solvent system comprises purified water or an alcohol, preferably ethanol

which may be denatured, for example, with butanone. The amounts of solids, *i.e.* galantamine.HBr and water-soluble polymer, in the drug coating solution may range from 10 to 30% (w/w) and preferably is about 25 %. The solution is preferably stirred during the coating process.

5

The drug coating process (on an industrial scale) is conveniently conducted in a fluidized bed granulator (e.g. Glatt type WSG-30 or GPCG-30) equipped with a Wurster bottom spray insert (e.g. an 18 inch Wurster insert). Laboratory scale process development can be performed on a Glatt type WSG-1 with a 6 inch Wurster bottom insert. Obviously the process parameters depend on the equipment used.

10

The spraying rate should be regulated carefully. Too low a spraying rate can cause some spray drying of the drug coating solution and result in a loss of product. Too high a spraying rate will cause overwetting with subsequent agglomeration. Agglomeration being the most serious problem, lower spraying rates may be used initially, to be increased as the coating process proceeds and the particles grow larger.

15

The atomizing air pressure with which the drug coating solution is applied also influences the coating performance. Low atomizing air pressure results in the formation of larger droplets and an increased tendency toward agglomeration. High atomizing air pressure could conceivably carry the risk of spray drying the drug solution, but this was found not to be a problem. Consequently, atomizing air pressure may be set at nearly maximum levels.

20

Fluidizing air volume can be monitored by operating the exhaust air-valve of the apparatus and should be set in such a manner that optimum pellet circulation is obtained. Too low an air volume will cause insufficient fluidization of the pellets; too high an air volume will interfere with the pellet circulation due to countercurrent air streams developing in the apparatus. In the present process optimum conditions were obtained by opening the exhaust air valve to about 50% of its maximum and gradually increasing the opening thereof to about 60% of the maximum as the coating process proceeded.

25

30

The coating process is advantageously conducted by employing an inlet-air temperature ranging from about 50°C to about 55°C. Higher temperatures may speed up the process but have the disadvantage that solvent evaporation is so rapid that the coating liquid is not spread uniformly on the surface of the pellets resulting in the formation of a drug coating layer with high porosity. As the bulk volume of the coated pellets increases,

35

drug dissolution may decrease significantly to unacceptable levels. Obviously, the optimum process temperature will further depend on the equipment used, the nature of the core, the batch volume, the solvent and the spraying rate.

-
- 5 Parameter settings for optimum coating results are described in more detail in the example hereinafter. Running the coating process under those conditions was found to yield very reproducible results.

- 10 In order to decrease residual solvent levels in the pellets following application of the rate controlling membrane from an organic solution, the pellets can conveniently be dried in any suitable drying apparatus. Good results may be obtained using a vacuum tumbler-drier operated at a temperature from about 60°C to about 90°C, preferably about 80°C, a reduced pressure ranging from about 150-400 mbar (15-40 kPa), preferably 200-300 mbar (20-30 kPa), for at least 24 hours, preferably about 36 hours.
- 15 The vacuum tumbler-drier is conveniently rotated at its minimum speed, e.g. 2 to 3 rpm. After drying, the drug coated cores may be sieved.

The seal coat layer is applied to the drug coated cores in the fluidized bed granulator with Wurster bottom spray insert or in a powder coater. The seal coating solution can

- 20 be prepared by dissolving an appropriate amount of a seal coating polymer into a suitable solvent system. Such a system, is, e.g. purified water or an alcohol, preferably ethanol which may be denatured with, for example, butanone. The amount of seal coating polymer in the seal coating spraying solution may range from 5 to 10% (w/w) and preferably is about 6.6%. The seal coating spraying solution is advantageously
- 25 stirred during the seal coating process. Appropriate conditions are described in more detail in the example hereinafter.

- 30 A further drying step may be required after applying the seal coating polymer layer. Excess solvents could easily be removed while operating the apparatus at the parameter settings used for about 5 to 15 minutes after the spraying had been completed.

- 35 The release rate controlling membrane coating polymer layer is applied to the drug (or seal) coated cores in a fluidized bed granulator with Wurster bottom spray insert. The release rate controlling membrane coating suspension or solution can be prepared by suspending or dissolving an appropriate amount of a release rate controlling membrane coating polymer into a suitable solvent system. Such a system, is, e.g. purified water or an alcohol, preferably ethanol which may be denatured with, for example, butanone, dichloromethane which may be admixed with an alcohol, preferably methanol or

ethanol. The amount of release rate controlling membrane coating polymer in the spraying suspension or solution may range from 5 to 40% (w/w) and preferably is about 30%. The release rate controlling membrane coating spraying suspension or solution is advantageously stirred during the spraying process. The parameter setting for
5 conducting this last step is essentially similar to that used in the previous coating processes. Appropriate conditions are described in more detail in the example hereinafter.

All coating processes are preferably conducted under an inert atmosphere of *e.g.*
10 nitrogen. The coating equipment should preferably be grounded and provided with an appropriate solvent recovery system containing an efficient condensing system.

The particles may be filled in hard-gelatin capsules using standard automatic capsule filling machines. Suitable earthing and de-ionisation equipment can advantageously
15 prevent development of electrostatic charges.

Capsule filling speed may influence weight distribution and should be monitored. Good results are obtained when operating the equipment at about 75% to 85% of the maximum speed and in many cases when operating at full speed.
20

Dosage forms according to the present invention having an advantageous pharmacokinetic profile as outlined, namely a fast onset and level peak and trough values, are capable of releasing in 500 ml USP buffer (pH 6.8) at 37°C in an Apparatus 2 (USP 23, <711> Dissolution, pp 1791-1793, paddle, 50 rpm) from 20 to 40 % of the
25 total amount of galantamine.HBr in 1 hour, and more than 80 % of the total amount of galantamine.HBr in 10 hours. Said dosage forms provide a mean maximum plasma concentration of galantamine from 10 to 60 ng/ml and a mean minimum plasma concentration from 3 to 15 ng/ml after repeated administration every day through steady-state conditions.
30

The formulations according to the present invention deliver a therapeutically effective amount of galantamine to a patient during the 24 hours following a single once daily administration.

35 The present invention also concerns pharmaceutical packages suitable for commercial sale comprising a container, a formulation of galantamine as claimed in claim 1, and associated with said package written matter specifying how said formulation should be administered.

Said pharmaceutical packages may be adapted for titrating a patient who is 'acetylcholine esterase inhibitor'-naïve, i.e. a patient who has not been exposed to an acetylcholine esterase inhibitor before and who should start with small, well-tolerated doses before being exposed to ever higher doses until the optimal dose is reached. Said

- 5 packages typically comprises 21-35 daily sequential dosage units of
- (a) a first group of 7 to 14 dosage units comprising from 5 to 10 mg galantamine,
 - (b) a second group of 7 to 14 dosage units comprising from 10 to 20 mg galantamine,
 - (c) a third group of 7 to 14 dosage units comprising from 15 to 30 mg galantamine, and
 - (d) optionally a fourth group of 7 dosage units comprising from 20 to 40 mg
- 10 galantamine.

- Alternatively, the pharmaceutical packages may be adapted for treating a patient who is 'acetylcholine esterase inhibitor'-tolerant, i.e. a patient who has been exposed to an acetylcholine esterase inhibitor before and who tolerates an optimal dose. Said
- 15 packages typically comprises daily dosage units comprising from 15 to 30 mg galantamine.

- A method of treating Alzheimer's dementia and related dementias in a human while substantially reducing (avoiding) the concomitant liability of adverse effects associated
- 20 with acetyl cholinesterase inhibitors, comprising administering to a human in need of such treatment, a therapeutically effective amount of galantamine in a controlled release formulation as claimed in claim 1, said amount being sufficient to alleviate said Alzheimer's dementia and related dementias, but insufficient to cause said adverse effects.

- 25 The related dementia belongs to the group consisting of vascular dementia, Lewy body disease, autism, mental retardation, bipolar disorder psychiatric conditions, disruptive behaviour, attention deficit hyperactivity disorder, substance abuse, extreme aggression, especially conduct disorder, nicotine cessation and withdrawal.

- 30 The adverse effects belong to the group comprising nausea, vomiting, sweating, restlessness, and insomnia.

Experimental partExample 1 : 8 mg galantamine CR oral capsule (F1)*Ingredients :*

	galantamine hydrobromide	10.253 mg (8 mg galantamine base)	
5	sugar spheres (18-20 mesh)	63.283 mg	
	HPMC 2910 5 mPa.s	1.465 mg	
	purified water	37.105 µl	*
	HPMC 2910 5 mPa.s	1.500 mg	
	polyethylene glycol 400	0.150 mg	
10	purified water	23.350 µl	*
	ethylcellulose aqueous dispersion	10.220 mg	(30 %)
	dibutyl sebacate	0.736 mg	
	purified water	10.220 µl	*
	capsule nr. 4		
15	* : these ingredients do not occur in the end product		

Preparation :

a) Drug coat suspension

Galantamine hydrobromide (123 g) was suspended in 297 ml purified water and heated to 70 -80 °C. HPMC 2910 5 mPa.s (17.58 g) was dissolved in the heated suspension whilst stirring.

b) Seal coat solution

Purified water (93.4 g) was heated to 70 - 80°C and HPMC 2910 5 mPa.s (18 g) and polyethylene glycol 400 (1.8 g) were dissolved therein. The solution was then further diluted with purified water (186.8 g).

c) Release rate controlling membrane coat dispersion

To a gently stirred aqueous dispersion of ethylcellulose (122.6 g ; 30 %) was added dibutyl sebacate (8.832 g). The dispersion was diluted with purified water (122.6 g).

d) Coating process

A fluidized-bed granulator (Glatt, type WSG 1) equipped with a 6 inch Wurster (bottom spray) insert was loaded with 18-20 mesh sugar spheres (759.4 g). The spheres were warmed with dry air of about 50°C. The fluidizing air volume was controlled by opening the exhaust air valve to approximately 45 % of its maximum. The drug coat suspension was sprayed on the spheres moving in the apparatus. The suspension was sprayed at a delivery rate of about 5 to 30 g.min⁻¹ at an atomizing air pressure of about 1.6 to 4.0 bar (0.16 -0.4 MPa). When the spraying process was completed, the coated spheres were dried by further supplying dry air of 60°C for about 2 minutes. The

coated spheres were then seal coated with the sealcoat solution using the same parameters as used in the drug coating process. After drying for about 2 minutes, the seal coated spheres were allowed to cool to room temperature and filled into a stainless steel drum.

- 5 The fluidized-bed granulator (Glatt, type WSG 1) equipped with a 6 inch Wurster (bottom spray) insert was reloaded with the seal coated spheres. The spheres were warmed with dry air of about 50°C. The fluidizing air volume was controlled by opening the exhaust air valve to approximately 45 % of its maximum. The release rate controlling membrane coat suspension was sprayed on the spheres moving in the
- 10 apparatus. The suspension was sprayed at a delivery rate of about 5 to 30 g.min⁻¹ at an atomizing air pressure of about 1.6 to 4.0 bar (0.16 -0.4 MPa). After drying for about 2 minutes, the controlled release membrane coated spheres were allowed to cool to room temperature and filled into a stainless steel drum.

e) drying and curing process

- 15 In order to remove agglomerates, the coated spheres were sieved using a sieve having a mesh width of 1.2 mm. The particles were placed in a drying oven at 60°C during 2 hours so as to cure the release rate controlling membrane.

f) capsule filling

- 20 The particles were filled into hard-gelatin capsules (size 4) using standard automatic capsule filling machines (e.g. Model GFK-1500, Höfflinger and Karg, Germany). In order to obtain capsules with good weight distribution, capsule filling speed was reduced to about 75-85% of the maximum speed. Each capsule received approximately 87.6 mg particles, equivalent to about 8 mg galantamine.

25 Example 2 : 8 mg galantamine CR oral capsule (F2)

Ingredients :

- | | | | |
|----|-----------------------------------|-----------------------------------|--------|
| | galantamine hydrobromide | 10.253 mg (8 mg galantamine base) | |
| | sugar spheres (18-20 mesh) | 63.283 mg | |
| | HPMC 2910 5 mPa.s | 1.465 mg | |
| 30 | purified water | 37.105 µl | * |
| | HPMC 2910 5 mPa.s | 1.500 mg | |
| | polyethylene glycol 400 | 0.150 mg | |
| | purified water | 23.350 µl | * |
| | ethylcellulose aqueous dispersion | 25.550 mg | (30 %) |
| 35 | dibutyl sebacate | 1.840 mg | |
| | purified water | 25.550 µl | * |
| | capsule nr. 4 | | |

* : these ingredients do not occur in the end product

Preparation :

5 The preparation was identical to that described in Example 1 except for the preparation of the release rate controlling membrane dispersion.

c) Release rate controlling membrane coat dispersion

10 To a gently stirred aqueous dispersion of ethylcellulose (306.6 g ; 30 %) was added dibutyl sebacate (22.08 g). The dispersion was diluted with purified water (306.6 g).

Example 3: Bioavailability

15 The bioavailability of a single oral administration of the two controlled release formulations of examples 1 and 2 was compared with that of an immediate release tablet (F3) [WO-97/47304] comprising 4 mg galantamine which was administered twice daily with an interval of 8 hours. Galantamine plasma levels in healthy volunteers (12) were determined by HPLC and the mean values calculated from the individual measurements are reported in the following table.

time (h)	F1	F2	F3
0	nd	nd	nd
0.5	1.6	nd	16.4
1	7.3	nd	24.1
1.5	11.5	nd	20.3
2	16.3	1.8	18.3
3	23.8	3.7	16.9
4	26.7	6.3	14.5
6	25.2	9.5	11.3
8	22.5	10.5	9.3
8.5			18
9			24.5
9.5			25.5
10	18.6	11.1	23.7
11			22.7
12	15.1	12.0	19.3
14	13.4	12.4	15.2
16	10.8	11.7	12.7
24	6.0	8.8	6.6

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time (h)	F1	F2	F3
30	3.5	6.1	3.5
36	2.0	4.3	2.0
48	nd	1.6	nd

nd : not detectable (< 1 ng/ml)

Example 4 : oral capsule (F4) comprising 8 mg galantamine
(75 % CR pellets and 25 % IR tablet)

Ingredients :

5	sugar spheres (18-20 mesh)	63.482 mg	
	galantamine hydrobromide	7.69 mg (6 mg galantamine base)	
	HPMC 2910 5 mPa.s	0.641 mg	
	purified water	42.932 µl	*
	HPMC 2910 5 mPa.s	1.436 mg	
10	polyethylene glycol 400	0.145 mg	
	methylene chloride	12.385 µl	*
	ethanol 96 % (v/v)	10.858 mg	*
	HPMC 2910 5 mPa.s	1.101 mg	
	ethylcellulose 20 mPa.s	3.308 mg	
15	diethyl phthalate	0.881 mg	
	methylene chloride	31.077 µl	*
	ethanol 96 % (v/v)	27.244 mg	*
	galantamine hydrobromide	2.563 mg (2 mg galantamine base)	
	spray-dried mixture of lactose monohydrate		
20	and microcrystalline cellulose (75:25)	49.302 mg	
	colloidal anhydrous silica	0.11 mg	
	croscopolvidone	2.750 mg	
	magnesium stearate	0.275 mg	

25 * : these ingredients do not occur in the end product

Preparation :

a) Drug layer suspension

Galantamine hydrobromide was suspended in purified water and heated to 70 -80 °C.

30 HPMC 2910 5 mPa.s was dissolved in the heated suspension whilst stirring.

b) Seal coat solution

Methylene chloride and ethanol were mixed together and polyethylene glycol and HPMC 2910 5 mPa.s were dissolved therein.

5 c) Release rate controlling membrane coat solution

Methylene chloride and ethanol were mixed and ethylcellulose 20 mPa.s, HPMC 2910 5 mPa.s and diethyl phthalate were added while stirring the solution.

d) Layering and coating process

10 A fluidized-bed granulator (Glatt) equipped with a Wurster (bottom spray) insert was loaded with 18-20 mesh sugar spheres. The spheres were warmed with dry air of about 50°C. The fluidizing air volume was controlled by opening the exhaust air valve to approximately 45 % of its maximum. The drug layer suspension was sprayed on the spheres moving in the apparatus. When the spraying process was completed, the layered
15 spheres were dried by further supplying dry air of 60°C for about 2 minutes. The layered spheres were then seal coated with the seal coat solution using the same parameters as used in the drug coating process. After drying for about 2 minutes, the seal coated spheres were allowed to cool to room temperature and filled into a stainless steel drum.

20 The fluidized-bed granulator (Glatt) equipped with a Wurster (bottom spray) insert was reloaded with the seal coated spheres. The spheres were warmed with dry air of about 50°C. The fluidizing air volume was controlled by opening the exhaust air valve to approximately 45 % of its maximum. The release rate controlling membrane coat suspension was sprayed on the spheres moving in the apparatus. After drying for about
25 2 minutes, the controlled release membrane coated spheres were allowed to cool to room temperature, sieved and filled into a stainless steel drum.

e) immediate release minitab

Galantamine hydrobromide, spray-dried mixture of lactose monohydrate
30 and microcrystalline cellulose (75:25), colloidal anhydrous silica, croscopolyvidone and magnesium stearate were mixed in a planetary mixer and compressed in a tableting machine, thus preparing minitab

f) capsule filling

35 The coated spheres and the immediate release minitab were filled into hard-gelatin capsules (size 0) using standard automatic capsule filling machines (e.g. Model GFK-1500, Höfflinger and Karg. Germany).

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Example 5 : galantamine oral capsules (F5, F6, F7, F8)
(75 % CR pellets and 25 % IR topcoat)

Ingredients :

	sugar spheres (18-20 mesh)	63.624 mg	
5	galantamine hydrobromide	7.69 mg (6 mg galantamine base)	
	HPMC 2910 5 mPa.s and PEG 400	12.687 mg (Opadry™ OY-7240 Clear, Colorcon)	
	purified water	267.693 µl	*
	HPMC 2910 5 mPa.s	1.260 mg	
	ethylcellulose 20 mPa.s	3.780 mg	
10	diethyl phthalate	1.008 mg	
	methylene chloride	46.772 µl	*
	ethanol 96 % (v/v)	31.184 mg	*
	galantamine hydrobromide	2.563 mg (2 mg galantamine base)	
	HPMC 2910 5 mPa.s and PEG 400	4.229 mg (Opadry OY-7240 Clear)	
15	purified water	89.321 µl	*
	capsules size nr. 4, 2, 1 and 0.		

*: these ingredients do not occur in the end product

20 *Preparation :*

a) Drug coat solution

Galantamine hydrobromide and Opadry OY-7240 Clear were dissolved in purified water at room temperature.

25 b) Release rate controlling membrane coat solution

Methylene chloride and ethanol were mixed and ethylcellulose 20 mPa.s, HPMC 2910 5 mPa.s and diethyl phthalate were added while stirring the solution.

c) Drug topcoat solution

30 Galantamine hydrobromide and Opadry™ OY-7240 Clear were dissolved in purified water at room temperature.

d) Coating process

35 A fluidized-bed granulator (Glatt) equipped with a Wurster (bottom spray) insert was loaded with 18-20 mesh sugar spheres. The spheres were warmed with dry air of about 50°C. The fluidizing air volume was controlled by opening the exhaust air valve to approximately 45 % of its maximum. The drug coat solution was sprayed on the

spheres moving in the apparatus. When the spraying process was completed, the coated spheres were dried by further supplying dry air of 60°C for about 2 minutes. The release rate controlling membrane coat solution was sprayed on the spheres moving in the apparatus. After drying for about 2 minutes, the controlled release membrane coated spheres were sprayed with the drug topcoat solution. After drying for about 2 minutes, the topcoated spheres were allowed to cool to room temperature, sieved and were filled into a stainless steel drum.

e) capsule filling

- 10 The topcoated spheres (96.841 mg ; 193.683 mg ; 290.524 ; 387.365 mg) were filled into hard-gelatin capsules (size numbers 4, 2, 1, 0) using standard automatic capsule filling machines (e.g. Model GFK-1500, Höfflinger and Karg. Germany) yielding oral capsules containing respectively 8 mg, 16 mg, 24 mg and 32 mg galantamine base.

- 15 Example 6 : galantamine oral capsules (F9)
(75 % CR pellets and 25 % IR topcoat)

Spheres having slightly faster release were made by lowering the ratio of ethylcellulose 20 mPa.s to HPMC 2910 5 mPa.s to 72.5 : 27.5 (as compared to the ratio 75 : 25 in the previous example.

20 Example 7 : *In vitro* dissolution of the topcoated spheres

Comparative *in-vitro* dissolutions studies were performed on the topcoated spheres formulations F5 to F8 and F9. The medium was 500 ml of USP buffer pH 6.8 at 37°C in Apparatus 2 (USP 23, <711> Dissolution, pp. 1791-1793) (paddle, 50 rpm).

- 25 The following results were obtained :

F5 to F8

Time (min)	Calculated concentration (% w/w) of the active dose						
	sample 1	sample 2	sample 3	sample 4	sample 5	sample 6	average
0	0.00	0.00	0.00	0.00	0.00	0.00	0.00
60	32.20	30.44	37.47	30.44	30.44	38.05	33.17
120	42.54	41.37	48.39	41.37	42.54	42.54	43.13
240	58.93	60.10	65.96	61.27	61.27	61.27	61.47
480	85.47	80.20	84.30	81.96	81.37	80.79	82.35
720	91.52	90.35	97.37	99.13	92.11	87.42	92.98
1080	96.59	97.18	102.45	102.45	99.52	98.94	99.52
1410	96.40	97.57	103.42	103.42	100.5	101.08	100.40

F9

Time (min)	Calculated concentration (% w/w) of the active dose						
	sample 1	sample 2	sample 3	sample 4	sample 5	sample 6	average
0	0.00	0.00	0.00	0.00	0.00	0.00	0.00
60	38.9	36.0	36.5	39.5	33.4	37.2	32.86
120	60.3	55.7	56.9	60.4	60.9	55.1	58.2
240	89.5	81.8	86.2	86.7	91.2	84.0	86.6
480	103.4	103.6	95.9	101.7	100.8	105.8	101.9
720	107.0	99.0	104.0	103.1	109.1	100.8	103.8

Claims

1. A controlled release formulation containing galantamine as the active ingredient, characterized in that it comprises particles comprising galantamine or a pharmaceutically acceptable acid addition salt thereof, a water soluble pharmaceutically acceptable excipient and optionally other pharmaceutically acceptable excipients, said particles being coated by a release rate controlling membrane coating.
2. A formulation according to claim 1 wherein galantamine is in the form of galantamine hydrobromide (1:1).
3. A formulation according to claim 1 wherein the water soluble excipient is a film forming polymer.
4. A formulation according to claim 3 wherein the water soluble film forming polymer is a polymer that has an apparent viscosity of 1 to 100 mPa.s when dissolved in a 2 % aqueous solution at 20°C solution.
5. A formulation according to claim 4 wherein the water soluble polymer is selected from the group comprising
 - alkylcelluloses such as methylcellulose,
 - hydroxyalkylcelluloses such as hydroxymethylcellulose, hydroxyethylcellulose,
 - hydroxypropylcellulose and hydroxybutylcellulose,
 - hydroxyalkyl alkylcelluloses such as hydroxyethyl methylcellulose and hydroxypropyl methylcellulose,
 - carboxyalkylcelluloses such as carboxymethylcellulose,
 - alkali metal salts of carboxyalkylcelluloses such as sodium carboxymethylcellulose,
 - carboxyalkylalkylcelluloses such as carboxymethylethylcellulose,
 - carboxyalkylcellulose esters,
 - starches,
 - pectines such as sodium carboxymethylamylopectine,
 - chitine derivates such as chitosan,
 - polysaccharides such as alginic acid, alkali metal and ammonium salts thereof, carrageenans, galactomannans, traganth, agar-agar, gummi arabicum, guar gummi and xanthan gummi,

- polyacrylic acids and the salts thereof,
 - polymethacrylic acids and the salts thereof, methacrylate copolymers,
 - polyvinylalcohol,
 - ~~polyvinylpyrrolidone, copolymers of polyvinylpyrrolidone with vinyl acetate~~
-
- 5 - polyalkylene oxides such as polyethylene oxide and polypropylene oxide and copolymers of ethylene oxide and propylene oxide.
6. A formulation according to claim 5 wherein the water soluble polymer is hydroxypropyl methylcellulose HPMC 2910 5 mPa.s.
- 10 7. A formulation according to claim 6 wherein the weight-by-weight ratio of hydroxypropyl methylcellulose HPMC 2910 5 mPa.s to galantamine is in the range of 17 : 1 to 1 : 5.
- 15 8. A formulation according to claim 2 wherein galantamine hydrobromide (1:1) and the water soluble, film forming polymer are layered or coated on an inert sphere.
9. A formulation according to claim 8 wherein the inert spheres are 16-60 mesh (1,180-250 • m) sugar spheres (NF XVII, page 1989).
-
- 20 10. A formulation according to claim 1 wherein the release rate controlling membrane coating comprises a water insoluble polymer and optionally a plasticizer.
11. A formulation according to claim 10 wherein the water insoluble polymer is ethylcellulose and the plasticizer is selected from the group comprising dibutyl sebacate, diethyl phthalate and triethyl citrate.
- 25 12. A formulation according to claim 11 wherein the weight of the release rate controlling membrane coating ranges from 3 % to 15 % of the uncoated particle.
- 30 13. A formulation according to claim 1 wherein a seal coat lies between the drug core and the release rate controlling membrane coating.
14. A formulation according to any one of claims 1 to 13 further comprising a topcoat comprising galantamine and water-soluble polymer.
- 35 15. A formulation according to claim 14 capable of releasing in USP buffer pH 6.8 at 37°C in an Apparatus 2 (USP 23, <711> Dissolution, pp 1791-1793, paddle, 50

rpm) from 20 to 40 % of the total amount of galantamine.HBr in 1 hour, and more than 80 % of the total amount of galantamine.HBr in 10 hours

- 5 16. A dosage form comprising a therapeutically effective amount of the controlled release formulation of any of claims 1 to 15.
- 10 17. A dosage form according to claim 16 which delivers a therapeutically effective amount of galantamine to a patient during the 24 hours following a single once daily administration.
- 15 18. A dosage form according to claim 16 wherein part of the galantamine is present in an immediate release form.
- 20 19. A dosage form according to claim 18 wherein said immediate release form comprises particles as described in claim 1 lacking the release rate controlling membrane.
- 25 20. A dosage form according to claim 18 wherein said immediate release form comprises immediate release minitabets.
- 30 21. A dosage form according to claim 18 wherein said immediate release form comprises a controlled release formulation of claim 14.
- 35 22. A dosage form according to claim 16 providing a mean maximum plasma concentration of galantamine from 10 to 60 ng/ml and a mean minimum plasma concentration from 3 to 15 ng/ml after repeated administration every day through steady-state conditions.
23. A pharmaceutical package suitable for commercial sale comprising a container, a formulation of galantamine as claimed in claim 1, and associated with said package written matter specifying how said formulation should be administered.
24. A pharmaceutical package as claimed in claim 23 adapted for titrating a patient who is 'acetylcholine esterase inhibitor'-naïve, characterized in that said package comprises 21-35 daily sequential dosage units of
 - (a) a first group of 7 to 14 dosage units comprising from 5 to 10 mg galantamine,
 - (b) a second group of 7 to 14 dosage units comprising from 10 to 20 mg galantamine,

- (c) a third group of 7 to 14 dosage units comprising from 15 to 30 mg galantamine, and
(d) optionally a fourth group of 7 dosage units comprising from 20 to 40 mg galantamine.
-

5

25. A pharmaceutical package as claimed in claim 23 adapted for treating a patient who is 'acetylcholine esterase inhibitor'-tolerant, characterized in that said package comprises daily dosage units comprising from 15 to 30 mg galantamine.
- 10 26. A process of preparing a formulation according to claim 1 comprising admixing galantamine or a pharmaceutically acceptable salt form thereof with a water soluble excipient to form a drug core, optionally applying a seal coat to the drug core, and thereafter applying the release rate controlling membrane coating.
- 15 27. A method of treating Alzheimer's dementia and related dementias in a human while substantially reducing (avoiding) the concomitant liability of adverse effects associated with acetyl cholinesterase inhibitors, comprising administering to a human in need of such treatment, a therapeutically effective amount of galantamine in a controlled release formulation as claimed in claim 1, said amount being
-
- 20 sufficient to alleviate said Alzheimer's dementia and related dementias, but insufficient to cause said adverse effects.
28. A method according to claim 27 wherein the related dementia belongs to the group consisting of vascular dementia, Lewy body disease, autism, mental retardation, 25 bipolar disorder psychiatric conditions, disruptive behaviour, attention deficit, hyperactivity disorder, substance abuse, extreme aggression, especially conduct disorder, nicotine cessation and withdrawal.
29. A method according to claim 27 wherein the adverse effects belong to the group 30 comprising nausea, vomiting, sweating, restlessness, and insomnia.

INTERNATIONAL SEARCH REPORT

International Application No
PCT/EP 99/10257

A. CLASSIFICATION OF SUBJECT MATTER
IPC 7 A61K31/55 A61P25/28 A61K9/54

According to International Patent Classification (IPC) or to both national classification and IPC

B. FIELDS SEARCHED

Minimum documentation searched (classification system followed by classification symbols)

IPC 7 A61K A61P

Documentation searched other than minimum documentation to the extent that such documents are included in the fields searched

Electronic data base consulted during the international search (name of data base and, where practical, search terms used)

C. DOCUMENTS CONSIDERED TO BE RELEVANT

Category *	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
Y	CA 1 326 632 A (DAVIS ET AL) 1 February 1994 (1994-02-01) cited in the application the whole document	1-12, 14, 16-18, 21, 26-29
Y	US 5 213 811 A (FRISBEE ET ASL.) 25 May 1993 (1993-05-25)	1-12, 14, 16-18, 21, 26-29
A	the whole document EP 0 629 402 A (BAYER AG) 21 December 1994 (1994-12-21) page 12; example 9	1, 10, 11

☐ Further documents are listed in the continuation of box C.

☒ Patent family members are listed in annex.

* Special categories of cited documents :

- "A" document defining the general state of the art which is not considered to be of particular relevance
- "E" earlier document but published on or after the international filing date
- "L" document which may throw doubts on priority claim(s) or which is cited to establish the publication date of another citation or other special reason (as specified)
- "O" document referring to an oral disclosure, use, exhibition or other means
- "P" document published prior to the international filing date but later than the priority date claimed

- "T" later document published after the international filing date or priority date and not in conflict with the application but cited to understand the principle or theory underlying the invention
- "X" document of particular relevance; the claimed invention cannot be considered novel or cannot be considered to involve an inventive step when the document is taken alone
- "Y" document of particular relevance; the claimed invention cannot be considered to involve an inventive step when the document is combined with one or more other such documents, such combination being obvious to a person skilled in the art.
- "&" document member of the same patent family

Date of the actual completion of the international search

11 May 2000

Date of mailing of the international search report

17/05/2000

Name and mailing address of the ISA
European Patent Office, P.B. 5818 Patentlaan 2
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Authorized officer

Benz, K

INTERNATIONAL SEARCH REPORT

International application No.

PCT/EP 99/10257

Box I Observations where certain claims were found unsearchable (Continuation of Item 1 of first sheet)

This International Search Report has not been established in respect of certain claims under Article 17(2)(a) for the following reasons:

1. ☒ Claims Nos.:
because they relate to subject matter not required to be searched by this Authority, namely:
Remark: Although claims 27-29 are directed to a method of treatment of the human/animal body, the search has been carried out and based on the alleged effects of the compound/composition.
2. ☐ Claims Nos.:
because they relate to parts of the International Application that do not comply with the prescribed requirements to such an extent that no meaningful International Search can be carried out, specifically:
3. ☐ Claims Nos.:
because they are dependent claims and are not drafted in accordance with the second and third sentences of Rule 6.4(a).

Box II Observations where unity of invention is lacking (Continuation of Item 2 of first sheet)

This International Searching Authority found multiple inventions in this international application, as follows:

1. ☐ As all required additional search fees were timely paid by the applicant, this International Search Report covers all searchable claims.
2. ☐ As all searchable claims could be searched without effort justifying an additional fee, this Authority did not invite payment of any additional fee.
3. ☐ As only some of the required additional search fees were timely paid by the applicant, this International Search Report covers only those claims for which fees were paid, specifically claims Nos.:
4. ☐ No required additional search fees were timely paid by the applicant. Consequently, this International Search Report is restricted to the invention first mentioned in the claims; it is covered by claims Nos.:

Remark on Protest

- ☐ The additional search fees were accompanied by the applicant's protest.
- ☐ No protest accompanied the payment of additional search fees.

INTERNATIONAL SEARCH REPORT

information on patent family members

International Application No

PCT/EP 99/10257


Patent document cited in search report	Publication date	Patent family member(s)	Publication date
CA 1326632 A	01-02-1994	CA 1338326 A AU 632458 B AU 1808488 A JP 2503794 T JP 2755403 B WO 8808708 A DK 549189 A EP 0363415 A FI 102756 B	14-05-1996 07-01-1993 06-12-1988 08-11-1990 20-05-1998 17-11-1988 03-01-1990 18-04-1990 15-02-1999
US 5213811 A	25-05-1993	NONE	
EP 629402 A	21-12-1994	DE 4319760 A AU 6345794 A CA 2125620 A CN 1099263 A CZ 9401464 A FI 942803 A HU 70759 A JP 6345649 A NO 942228 A NZ 260732 A PL 303822 A SK 72494 A ZA 9404187 A	22-12-1994 22-12-1994 16-12-1994 01-03-1995 18-01-1995 16-12-1994 30-10-1995 20-12-1994 16-12-1994 27-02-1996 09-01-1995 12-04-1995 08-02-1995

PATENT COOPERATION TREATY

PCT

INTERNATIONAL PRELIMINARY EXAMINATION REPORT

(PCT Article 36 and Rule 70)

Applicant's or agent's file reference JAB 1461-PCT		FOR FURTHER ACTION	See Notification of Transmittal of International Preliminary Examination Report (Form PCT/IPEA/416)
International application No. PCT/EP99/10257	International filing date (day/month/year) 20/12/1999	Priority date (day/month/year) 24/12/1998	
International Patent Classification (IPC) or national classification and IPC A61K31/55			
Applicant JANSSEN PHARMACEUTICA N.V. et al.			
<p>1. This international preliminary examination report has been prepared by this International Preliminary Examining Authority and is transmitted to the applicant according to Article 36.</p> <p>2. This REPORT consists of a total of 6 sheets, including this cover sheet.</p> <p><input type="checkbox"/> This report is also accompanied by ANNEXES, i.e. sheets of the description, claims and/or drawings which have been amended and are the basis for this report and/or sheets containing rectifications made before this Authority (see Rule 70.16 and Section 607 of the Administrative Instructions under the PCT).</p> <p>These annexes consist of a total of sheets.</p>			
<p>3. This report contains indications relating to the following items:</p> <ul style="list-style-type: none"> I <input checked="" type="checkbox"/> Basis of the report II <input type="checkbox"/> Priority III <input checked="" type="checkbox"/> Non-establishment of opinion with regard to novelty, inventive step and industrial applicability IV <input type="checkbox"/> Lack of unity of invention V <input checked="" type="checkbox"/> Reasoned statement under Article 35(2) with regard to novelty, inventive step or industrial applicability; citations and explanations supporting such statement VI <input type="checkbox"/> Certain documents cited VII <input type="checkbox"/> Certain defects in the international application VIII <input type="checkbox"/> Certain observations on the international application 			
Date of submission of the demand 15/05/2000		Date of completion of this report 27.03.2001	
Name and mailing address of the international preliminary examining authority:  European Patent Office D-80298 Munich Tel. +49 89 2399 - 0 Tx: 523656 epmu d Fax: +49 89 2399 - 4465		Authorized officer Giacobbe, S Telephone No. +49 89 2399 8463	



**INTERNATIONAL PRELIMINARY
EXAMINATION REPORT**

International application No. PCT/EP99/10257

I. Basis of the report

1. This report has been drawn on the basis of *(substitute sheets which have been furnished to the receiving Office in response to an invitation under Article 14 are referred to in this report as "originally filed" and are not annexed to the report since they do not contain amendments (Rules 70.16 and 70.17).):*

Description, pages:

1-19 as originally filed

Claims, No.:

1-29 as originally filed

2. With regard to the **language**, all the elements marked above were available or furnished to this Authority in the language in which the international application was filed, unless otherwise indicated under this item.

These elements were available or furnished to this Authority in the following language: , which is:

- ☐ the language of a translation furnished for the purposes of the international search (under Rule 23.1(b)).
☐ the language of publication of the international application (under Rule 48.3(b)).
☐ the language of a translation furnished for the purposes of international preliminary examination (under Rule 55.2 and/or 55.3).

3. With regard to any **nucleotide and/or amino acid sequence** disclosed in the international application, the international preliminary examination was carried out on the basis of the sequence listing:

- ☐ contained in the international application in written form.
☐ filed together with the international application in computer readable form.
☐ furnished subsequently to this Authority in written form.
☐ furnished subsequently to this Authority in computer readable form.
☐ The statement that the subsequently furnished written sequence listing does not go beyond the disclosure in the international application as filed has been furnished.
☐ The statement that the information recorded in computer readable form is identical to the written sequence listing has been furnished.

4. The amendments have resulted in the cancellation of:

- ☐ the description, pages:
☐ the claims, Nos.:
☐ the drawings, sheets:

5. ☐ This report has been established as if (some of) the amendments had not been made, since they have been considered to go beyond the disclosure as filed (Rule 70.2(c)):

INTERNATIONAL PRELIMINARY EXAMINATION REPORT

International application No. PCT/EP99/10257

(Any replacement sheet containing such amendments must be referred to under item 1 and annexed to this report.)

6. Additional observations, if necessary:

III. Non-establishment of opinion with regard to novelty, inventive step and industrial applicability

1. The questions whether the claimed invention appears to be novel, to involve an inventive step (to be non-obvious), or to be industrially applicable have not been examined in respect of:

☐ the entire international application.

☒ claims Nos. 1, 27-29.

because:

☒ the said international application, or the said claims Nos. 27-29 relate to the following subject matter which does not require an international preliminary examination (*specify*):
see separate sheet

☐ the description, claims or drawings (*indicate particular elements below*) or said claims Nos. are so unclear that no meaningful opinion could be formed (*specify*):

☒ the claims, or said claims Nos. 1 are so inadequately supported by the description that no meaningful opinion could be formed.

☐ no international search report has been established for the said claims Nos. .

2. A meaningful international preliminary examination report cannot be carried out due to the failure of the nucleotide and/or amino acid sequence listing to comply with the standard provided for in Annex C of the Administrative Instructions:

☐ the written form has not been furnished or does not comply with the standard.

☐ the computer readable form has not been furnished or does not comply with the standard.

V. Reasoned statement under Article 35(2) with regard to novelty, inventive step or industrial applicability; citations and explanations supporting such statement

1. Statement

Novelty (N) Yes: Claims 1-29
 No: Claims

Inventive step (IS) Yes: Claims 1-29
 No: Claims

Industrial applicability (IA) Yes: Claims 1-26

**INTERNATIONAL PRELIMINARY
EXAMINATION REPORT**

International application No. PCT/EP99/10257

No: Claims 27-29 (see Separate Sheet)

2. Citations and explanations
see separate sheet

**INTERNATIONAL PRELIMINARY
EXAMINATION REPORT - SEPARATE SHEET**

International application No. PCT/EP99/10257

1. Section III

1.1 Claims 27-29 relate to subject-matter considered by this Authority to be covered by the provisions of Rule 67.1(iv) PCT. Consequently, no opinion will be formulated with respect to the industrial applicability of the subject-matter of these claims (Article 34(4)(a)(i) PCT). However, although not required under the provisions of the PCT, an opinion will be given with respect to novelty and inventive step.

1.2 Independent claim 1 broadly defines the essential feature of the invention in terms of its function, namely that of being a release rate controlling membrane. However, the description (cf. p. 6, ll. 6-9) conveys the impression that this function can only be carried out by one particular substance, namely ethylcellulose, and no alternative means are envisaged. Hence, claim 1 is not supported by the description as required by Article 6 PCT. Only those parts of the application which are supported by the description have been examined.

2. Section V

2.1 Cited Documents

The following document (D) is referred to in this Report:

D1: US-A-5 213 811 (FRISBEE ET ASL.) 25 May 1993

2.2 Art 33(2) PCT (Novelty)

The subject-matter of present claims 1-29 meets the requirements of Art 33(2) PCT.

2.3 Art 33(3) PCT (Inventive step)

The subject-matter of present claims 1-29 meets the requirements of Art 33(3) PCT.

Document D1, which is considered to represent the most relevant state of the art, discloses (cf. column 1 ll. 38-51) sustained release formulations for drugs where the active principle is adhered onto an inert core and then surrounded by a sustaining coating comprising at least three polymers, among which is also ethylcellulose, each of which has a different role depending on the pH at which it dissolves. The technical problem which the present application sought to solve vis-à-vis this particular prior art document can therefore be seen as "how to provide a sustained release formulation for galantamine". The solution proposed involves an inventive step since this document does not suggest that ethylcellulose alone can provide the sustained release coating for

**INTERNATIONAL PRELIMINARY
EXAMINATION REPORT - SEPARATE SHEET**

International application No. PCT/EP99/10257

the specific drug galantamine.

2.4 Art 33(4) PCT (Industrial applicability)

As stated above, no opinion is given on the question of whether present claims 27-29 are industrially applicable since their patentability is inter alia dependent upon their formulation as well as upon national and regional laws and no unifying criteria is provided in this field by the PCT.

3. Section VII

Claims 6 and 7 contain terms which appear to be registered trade marks and which are not internationally accepted as standard descriptive terms, thereby rendering the definition of the subject-matter of these claims unclear (Article 6 PCT).

4. Section VIII

Claims 9 and 15 contain unallowable references to textbooks.
